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MORPHOLOGICAL CHANGES OF SYNAPTIC FORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN EXPERIMENTAL CHRONIC RADIATION SICKNESS (1)

/Following is the translation of an article by A. G. Khanin entitled "O Morfologicheskikh Izmeneniyakh Sinapticheskikh Obrazovaniy Tsentral'noy Nervnoy Systemy pri Eksperimental'noy Luchevoy Bolezni" (English version above) in Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Journal of Neuropathology and Psychiatry im S. S. Korsakov), Vol. 60, No. 5, Moscow 60, pages 522-528./

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Studies were carried out on 14 dogs (nine experimental and five controls), two to four years of age, 14 to 18 kw in weight. The dogs were exposed daily (except on rest-days) to a total bilateral X-ray irradiation by means of two RUM-3 apparatus with a 15 r dose for two minutes at 120 cm focal distance and physical power of the two apparatus seven to eight r/min. The tube voltage was 180 kV, current strength -- 15 mA; filter -- 0.5 mm cuprum and one mm ∕ aluminum.

A certain number of dogs were killed at various stages of chronic radiation sickness, others were subjected to an autopsy after death (terminal stage). Pieces of the brain and spinal cord were impregnated with silver by the Kakhal method with pyridine fixation, and paraffin sections were prepared. The cerebral tissue sections were also stained according to Nissl's method.

There were no microscopic changes noted in the brain in the first and second stages. In the third and fourth

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stages there was an uneven plethora of brain tissue and its membranes, a smoothing-out of the cerebral convolutions and flabbiness of its substance. In two cases there were extensive subdural hemorrhages on the convex surface of the brain. There were no discernible macroscopic changes in the spinal cord.

Studies of the sections of the brain and spinal cord of five healthy dogs showed axosomatic and axodendritic synaptic formations of monotypic structure; the presynaptic fibrils were thin, of uniform thickness along their entire length, with even edges and no tortuosity; the synaptic Auerbach-Held plaques were represented by characteristic small rings and loops of round or oval form with a light center and even contours. Button-like endings were encountered among them. The size of the plaques varied; there were encountered only isolated synaptic loops, about twice as large in their diameter as that of the basic mass of rings, and somewhat darker impregnated. One could see in the cerebral tissue a considerable number of plaques without presynaptic fibrils. The polymorphism of terminal formations was negligible. The dedritic processes with smooth, even contours were not tortuous. The neurofibrillary apparatus was lightly stained, the striated structure well expressed.

The cerebrum and spinal cord of two dogs (total dose of ionizing radiation 225 r) were examined in the first stage (the stage of initial phenomena, according to the clinical hematological indices).

The histopathological changes in the interneural structures of the cerebral hemispheres, brain stem and spinal cord were of an irritation type against the background of unaltered synaptic formations. In the neural cells and their dendritic processes there could be observed a coarse staining of the neurofibrillary apparatus and the disappearance of its striated character. The protoplasmic processes not infrequently appeared tortuous. The axosomatic and axodendritic ringlets and knobs were more polymorphous than normal and more intensively stained with silver. A large quantity of synaptic rings, enlarged in size, could be seen. In the presynaptic fibrils there was swelling and argyrophilia, varicose thickenings, and a tortuous course.

In the cortex of the cerebral hemispheres there were analogous pathological changes in the interneural terminal apparatus -- in the frontal, precentral, postcentral, parietal, occipito-parietal, occipital and limbic areas. In the cortical preparation, Nissl stained, there were observed changes in the minute groups of neural cells, as well as in isolated cells scattered in various areas. These changes were manifested by the altered staining of the chromatophis substance

and minute changes in the cellular structure. The protoplasm of a number of neural cells was slightly stained, the contours of the nucleus smoothed out. In the cortex there were encountered slightly swollen, lightly stained cells, as well as cells of irregular form. In the upper layers there were minute groups of pale, darkly stained neural cells (hypo- and hyperchromatic cells). Among the hyperchromatic cells of all layers there were isolated cells with slightly shrunken bodies and tortuous, somewhat thinned processes (phenomena of shriveling).

In the central and lateral nucleus and in the other nuclei of the thalamus opticus there was noted a certain irritation of the synaptic structures in the form of increased argyrophilia. Similar changes were also observed in the reticular substance of the diencephalon. In the subcortical notes? /nodes/ subthalamus and cornu Ammonis the irritation phenomena were insignificant and consisted of a certain coarsening and swelling of the fibers.

In the motor, sensory, and vegetative nuclei of the cerebrocranial nerves (third to 12th pair) there was observed in a number of neurons an increased argyrophilia of the neurofibrillary apparatus, as well as neuroplasms. In addition, there were often encountered swollen (evenly or unevenly) and varicosely changed presynaptic fibers. The synaptic plaques on the bodies and dendrites of the cells were more polymorphous than normal, often hypertrophied and solidly stained. In the reticular substance the affections /pathological changes/ of the synaptic ends were more clearly manifested than in other nuclei of the stem area of the brain and involved a considerable number of neurons.

In the cerebellum there was observed swelling and impregnation of the basket-like apparatus of Purkinje's cells, as well as of the fibrils of the stellate cells along the course of the axis cylinders of purkinje's cells.

In the gray matter of the spinal cord, as well as in the cerebrum, there were detected changes in the axosomatic and axodendritic bonds, the neurofibrillary apparatus, and the neuroplasm of the body and processes. We did not observe the predominance of affection of Clark columns, as described in acute radiation sickness by A. D. Zurabashvili and B. P. Naneyshvili /1/. On the Nissl-stained preparations from the subcortical nodes, brain stem, and spinal cord, hyper- and hypo-chromatic neural cells were encountered at times. In comparing synaptic endings of the motor (motor neurons of the spinal cord, motor nuclei of cerebrocranial nerves, neural cells of the precentral area), sensory (neurons of the dorsal horns of the spinal column, nuclei of the thin and wedge-shaped bundles, the ventral and lateral thalamic nuclei, the

postcentral cortical area) and vegetative formations of the cerebrum and spinal cord (dorsal nucleus of the vagus, supra-optic nucleus, sympathetic nucleus), as well as the reticular substance, in the control preparations from healthy animals and in the preparations from experimental animals we could not succeed in detecting any predominance in the affection of the synapses of any of these structures. The synaptic apparatus was better manifested in the motor cells and cells of the reticular substance, in which it was easier to study it.

In the second stage (stage of comparative clinical well-geing) we examined the cerebellum, medulla oblongata and various sections of the spinal cord of two dogs (total doses of ionizing radiation -- 480r and 510 r, duration of the experiment 38 and 40 days). Pathological changes of the terminal interneuron apparatus of bonds in this stage was manifested in approximately the same degree as in the first stage. Possibly some of the synaptic structures were restored, and at the same time certain still intact neuronal synapses became involved in the pathological process, as a result of which evidence of reactive changes was observed. The neurofibrillary apparatus and the neuroplasm of the body and processes of neural cells were often hyperimpregnated. Pathological changes were found in the terminal formations of the motor neurons, cells of Clarke and Schtilling, in the intermedial zone and the dorsal horns. The presynaptic fibrils along the course of the dendritic processes, as well as the fibrils approaching the neural cells, were swollen, coarsened, and highly argyrophilic. The synaptic plaques in a number of cells were not infrequently hypertrophied, argyrophilic and polymorphous. In addition, a polychromatic staining of a considerable number of small loops, was also observed i. e., various intensities of their staining with silver. In the cerebellum an increased argyrophilia of the basket apparatus of Purkinje's cells was observed.

Nissl staining of the cerebral tissue revealed hyper- and hypo-chromatic, as well as shriveled cells.

We examined the brains of two dogs in the third stage (stage of pronounced clinical manifestations); they had received total doses of irradiation amounting to 1650r and 1785r and had been subjected to the experiment for 130 and 140 days. The medullae oblongatae and spinal cords were examined histologically.

This stage was characterized by further development, extension, and intensification of reactive reversible changes of the terminal interneuronal structures, as well as the development of non-reversible degenerative-necrobiotic changes against this background. On the whole, however, the patho-

logical changes of the non-reversible type were much less in evidence than the reactive reversible changes, and the axo-somatic bonds were more easily affected than the axodendritic ones. Together with the changed synapses there could also be observed a considerable number of intact synaptic formations. Compensation-adaptation processes were only slightly manifested.

The increased argyophilia of the neurofibrillary apparatus and neuroplasm of the neurons, their bodies and protoplasmic processes was observed in a larger number of neural cells than in the second stage. The dendritic processes of a number of cells were tortuous in various degrees.

Against the background of an increase and greater expansion of reactive changes in the preterminal fibers there were manifested degenerative-necrobiotic changes in their structure, as the result of which the histological picture of affection of the fibers was very variegated.

Together with increased phenomena of swelling and argyrophilia there were also an increased number of hyperimpregnated evenly and unevenly swollen fibers, fibers with bead-like and varicose bulges and marked tortuosity (zigzag, serpent-like, serpent-like and at the same time bow-shaped, etc.) These changes involved the pericellular as well as the peridendritic fibers. In many synaptic structures phenomena of fragmentation were observed. Besides, near the dendrites fibers could be seen with lighter and interrupted segments (the fragmentation process). Most frequently the fragmented fibers were found in the pericellular zone and the bodies of neurons (Fig. 1). The fragmentation forms varied greatly: in the form of an elongated comma, rough rods, arc, segments, zigzag or serpent-like curve, fork, horseshoe, letter Л ; often the fragments had varicose or bead-like bulges. Their arrangement in relation to the neuron had a haphazard character. These changes in the preterminal fibers were widely distributed in the reticular substance and anterior horns of the medulla oblongata, in various horns of the spinal cord, intermedial zone, Clarke's column and in its reticular nucleus.

During the third stage a slightly manifested progressive reaction of a hyperplastic regenerative type was observed in the presynaptic fibers. Some presynaptic fibrils formed collaterals (of normal or hypertrophied structure), which created the impression of a synaptic little bush approaching, with its fibrils, the cellular body (Fig. 2). Phenomena of branching and collateralization of preterminal fibrils can be related to the proliferative, compensatory-adaptation changes, which contribute to the improvement of the innervation mechanism of the neurons under pathological conditions of

the synaptic structures. However, the collateralization phenomena were observed only in a small number of cells, therefore they apparently have a wide protective physiological importance, the more so in that the hyperplastic branches were not infrequently pathologically altered (hypertrophied).

The reactive changes in the terminal synaptic plaques of the cellular bodies and dendritic processes in the third stage assumed an even more demonstrative and extensive character; in contrast to the first two stages, degenerative-necrobiotic changes developed in them. The structural changes in the terminal plaques were characterized by strikingly manifested signs of swelling, hyperimpregnation, polymorphism and polychromia, deformation and disintegration (Figs. 1 and 2). Such changes were observed in the somatic and dendritic terminal plaques. The phenomena of marked deformation and breaking-up of synaptic plaques were first observed during the third stage. A considerable number of terminal knobs were deformed, and had angular, broken, scalloped contours. The deformation phenomena were observed in the hypertrophied plaques as well as in the small ones. They were widely distributed in all horns of the spinal cord and in the medulla oblongata (reticular substance, anterior horns). In the pericellular space and on the body of cells there were observed clumps of disintegrated plaques, as well as separation (fragmentation) of altered plaques from the presynaptic fibers. In a number of neural cells there was observed a heap-like arrangement of deformed, markedly argyrophilic plaques situated close to each other.

The extent of degenerative-necrobiotic changes in the neuronal synapses after ionizing irradiation depended on the resistance of the animal organism (the resistance was determined mainly by the dynamics of clinico-hematological indices). For instance, in a dog of average resistance with clinical symptoms of third-stage radiation sickness, after a total radiation dose of 1650 r and an experiment lasting 130 days, the degenerative-necrobiotic changes in the synaptic apparatus were more pronounced than in a dog with higher resistance and an analogous clinical symptom complex of radiation sickness, which had developed under comparable irradiation conditions (total dose 1785 r, duration of experiment 140 days).

Nissl staining of neural cells of the brain and spinal cord, presented a variegated picture of different histopathological changes of a reactive and degenerative-necrobiotic character. In the brain and spinal cord there were observed, in a considerable number of cells, phenomena of chromatolysis and vacuolation, acute swelling, cytolysis, and small areas of disappearance of neural cells with a mild reaction of glia

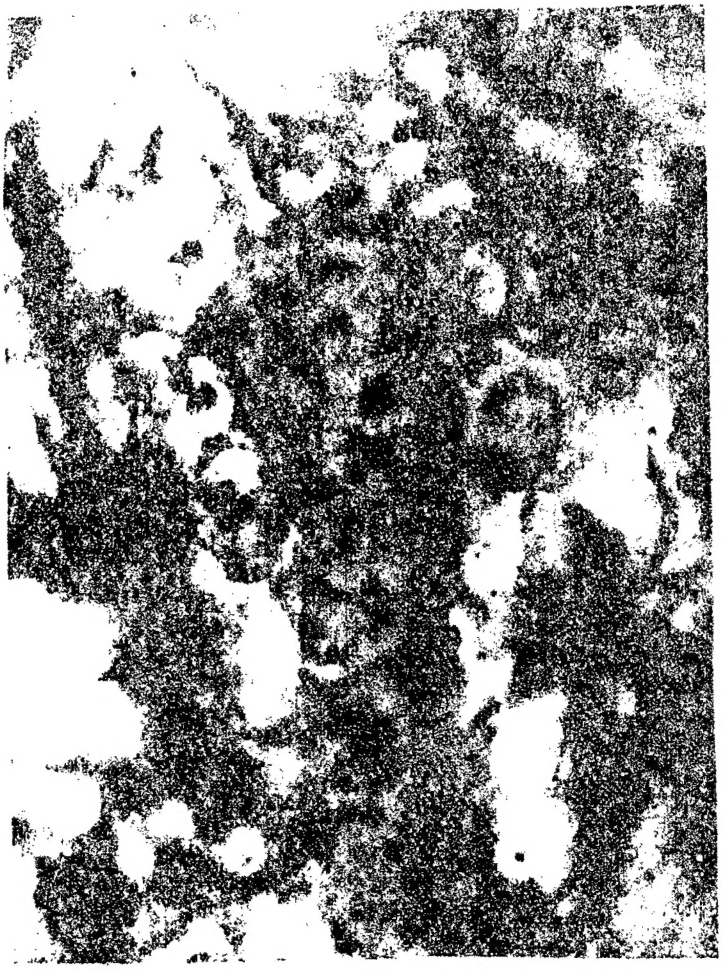

Fig. 1. Posterior lateral nucleus of the anterior horn of the thoracic section of the spinal cord. Fragmentation of presynaptic fibers. Polymorphism and hypertrophy of terminal plaques. Magnification: 1440 times. Total ionizing radiation dose 1650 r. Third stage of chronic radiation sickness.

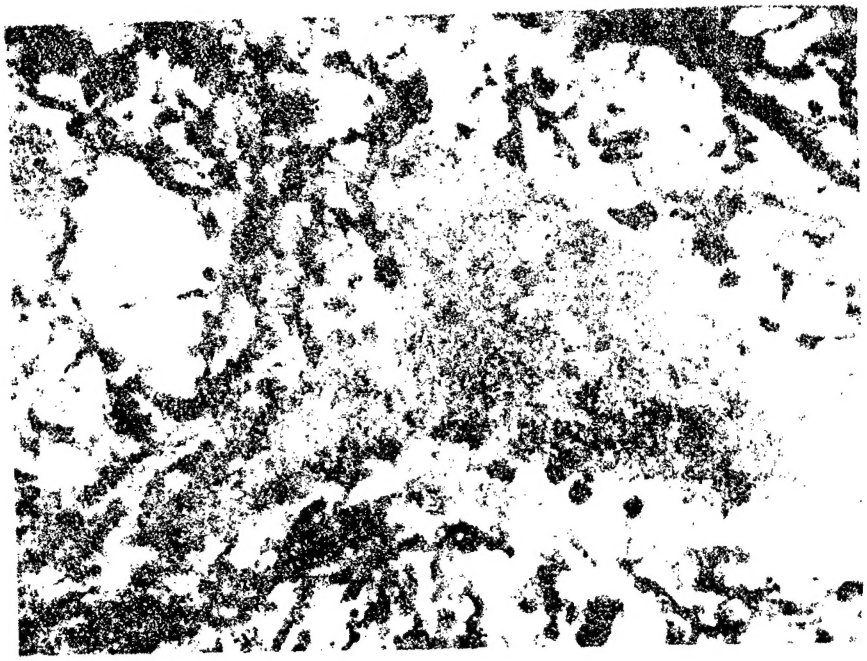

Fig. 2. Medio-lateral nucleus of the anterior horn of the thoracic section of the spinal cord. Marked polymorphism of synaptic endings. Fork-like branching of some presynaptic fibers.

Magnification: 1440 times. Total ionizing radiation dose 1785 r. Third stage of chronic radiation sickness.

cells. In addition, quite frequently small groups, or isolated hyperchromatic and shriveled (sclerotic) cells with corkscrew-like twisted processes were seen.

The spinal cords and medullae oblongatae of three dogs in the fourth stage (terminal), were subjected to study: two dogs had died after total doses of 1095r and 2175 r, having endured the experiment 85 and 169 days, respectively. The third dog was killed following a total dose of 1545 r, the experiment lasting 120 days.

Against the background of reactive changes of the synaptic structures, degenerative-necrobiotic changes continued to increase (swelling, varicose state, bead-like character and tortuosity of the presynaptic fibers, their fragmentation, and disintegration of terminal plaques), involving an ever greater number of cells. A considerable number of fibers, situated along the dendrites and near neural cells, underwent fragmentation. The argyrophilic fragments had various abnormal shapes, or appeared in the form of swollen clumps and grains. In a number of fragments of fibers there were minute spheroid swellings. On the dendrites and neural cells there were often observed hypertrophied plaques with remnants of presynaptic fibers, and disintegration grains of synaptic knobs were encountered. Among markedly changed presynaptic fibers and terminal plaques slightly altered synaptic apparatus were also seen. In the cerebral tissue one could also see morphologically intact synaptic structures.

The changes described were observed in the neural cells of all horns of the spinal cord and in the medulla oblongata (ventral nucleus of the supplementary nerve, the nucleus of the cuneiform bundle, the reticular substance and Rolando's gelatinous substance).

Changes in the synaptic formations of different animals were not uniform, depending on their resistance, the total ionizing radiation dose, and the duration of irradiation. Thus, in a dog with high resistance who had received a total irradiation dose of 2175 r and had been under experimental observation for 169 days, there were observed grave affections of the synaptic apparatus. On the other hand, in dogs of average or lower resistance, at total doses of 1545r and 1095 r, the experiment lasting 120 and 85 days, respectively, lesser pathological changes of the synaptic ends, approaching those of the third stage, were noted. These data indicate that, at a considerably higher total dose and longer duration of irradiation, the morphological changes of synapses in dogs with high resistance may be more markedly expressed than in dogs with average or lower resistance. In examining Nissl-stained preparations of the brain and spinal cord, we established that degenerative-necrobiotic changes extended to a

larger number of neural cells (chromatolysis, vacuolation, caryopicnosis, caryocytolysis, hyperchromia and sclerosis of cells), and the number of areas in the cerebral tissue where neural cells had disappeared showed an increase.

The results of histopathological studies of interneuronal synaptic bonds in the central nervous system during the development of an experimental chronic radiation disease enabled us to characterize the pathology of the synaptic neuron apparatus as a toxicodystrophy which develops by stages. The gravity of the dystrophic phenomena depended on the resistance of the organism to ionizing radiation, the total dose, and the duration of irradiation.

Analogous toxicodystrophic destructive changes in the synaptic formations of the central nervous system were described by M. S. Tolgskaya [2] in [?] cases of chronic intoxication with occupational poisons (lead, aniline, arsenic). This fact may serve as confirmation of the characterization of interneuron bonds pathology in experimental chronic radiation sickness as a toxicodystrophy.

These data show that the resistance of the synaptic apparatus to experimental chronic radiation sickness is relative. It depends on the stage of development of the disease, resistance of the animal, the total ionizing radiation dose, and the duration of irradiation. On the basis of their observations in acute radiation sickness, A. D. Zurabashvili and B. R. Naneyshvili [1], pointed out only the importance of the duration and strength of the effect of penetrating rays.

Pathological changes in the interneuronal structures during the first two stages are reversible. In the third and fourth stages, against the background of reactive, restorative changes, the non-reversible reaction component -- coarse necrobiotic changes -- can be easily observed.

In conclusion it is necessary to point out that in the literature devoted to morphological studies of acute radiation sickness, no attention has been paid to the dynamics of changes in the terminal interneuron structures; therefore there is a need to carry out investigations in this direction, as indicated by our data.

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